Study of the Safety and Efficacy of Neurostimulation of the Cholinergic Anti-Inflammatory Pathway Using a Vagal Nerve Stimulation Device in Patients with Active Refractory Crohn*s Disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON44525

Source
ToetsingOnline

Brief title
SPM-007

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease, Inflammatory Bowel Disease

Research involving
Human

Sponsors and support

Primary sponsor: SetPoint Medical Corporation
Source(s) of monetary or material Support: SetPoint Medical Corporation

Intervention

Keyword: Crohn's disease, Medical Device, Nerve, Stimulation

Outcome measures

Primary outcome

Primary Endpoint:

Change in CDAI from baseline to Week 16 Visit

Secondary outcome

Secondary Endpoints:

-Rate of clinical response at Week 16 Visit defined as CDAI improvement from

baseline of at least 70 points

-Rate of clinical remission at Week 16 Visit defined as CDAI less than or equal

to 150

-Change in IBDQ total score and subscale scores from baseline to Week 16 Visit

-Change in total SES-CD score from baseline to Week 16 Visit

-Endoscopic Response Rate: Percentage of patients with drop in total SES-CD

score of at least 50% from baseline to Week 16 Visit

-Endoscopic Remission Rate: Percentage of patients with no ulcers larger than

aphthous ulcers in any segment (i.e., all observed segments have an

ulcer score of
-Correlation between Heart Rate Variability High Frequency and Low Frequency

parameters at baseline and change in CDAI from baseline to Week 16 Visit

-Correlation between reduction in Whole Blood LPS-induced TNF Release after

Auricular Stimulation Screening and change in CDAI from baseline to Week 16

Visit

Study description

Background summary

There is already a significant amount of data (both pre-clinical and clinical) to show the benefit of neurostimulation of the cholinergic anti-inflammatory pathway using a vagal nerve stimulation device. Indeed a device is already on the market for patients suffering from epilepsy, and promising data exist from a recent clinical trial of the device in patients suffering from rheumatoid arthritis.At present, there is currently no cure for Crohn's disease, and palliative treatment with corticosteroids and immuno-suppressants are standard of care. The proposed study potentially offers a new way to treat this disease, and will examine the safety and efficacy of neurostimulation of the cholinergic anti-inflammatory pathway using a vagal nerve stimulation device in patients with active refractory Crohn*s disease

Study objective

Primary Efficacy Objective
The primary efficacy objective is to determine the effect of NCAP delivered by the implanted device on clinical signs and symptoms of Crohn*s disease, as assessed by the Crohn*s Disease Activity Index (CDAI)

Secondary Efficacy Objectives:
-Determine the effect of NCAP delivered by the implanted device on mucosal inflammation assessed by the Simple Endoscopic Score for Crohn*s Disease (SES-CD)
-Determine the effect of NCAP delivered by the implanted device on health-related quality of life as assessed by the inflammatory bowel disease questionnaire (IBDQ)
-Determine whether preoperative Heart Rate Variability (HRV) parameters correlate to clinical response to NCAP delivered by the implanted device
-Determine whether preoperative changes in Whole Blood LPS-Induced TNF Release Assay in response to non-invasive Auricular Stimulation Screening correlate to clinical response to NCAP delivered by the implanted device

Exploratory Efficacy Objectives:
-Determine the effect of NCAP delivered by the implanted device on health-related quality of life as assessed by the Simple Health Score instrument (SHS)

-Determine the effect of NCAP delivered by the implanted device on biomarkers of Crohn*s disease activity including:
• Fecal Calprotectin
• High Sensitivity C-Reactive Protein (hsCRP)
• Bone turnover markers (collagen type-1 C-terminal telopeptide (CTX-1), and type-1 procollagen N-terminal propeptide (P1NP))
• Serum Inflammatory Mediators (30 analyte multiplex)
• Endoscopic Biopsy Histology Score (Geboes score)
• Whole Blood LPS-induced TNF Release Assay
• Endoscopic Biopsy Expression of Inflammatory Mediators as Assessed by Immunohistochemistry, Quantitative PCR, and ELISA

Study design

This will be an open-label, multicenter study of the safety, biological activity and clinical outcome of an active implantable VNS device in patients with active refractory Crohn*s Disease. Patients will undergo all screening and baseline assessment procedures including endoscopy and endoscopic biopsy prior to planned VNS implantation date. After a minimum of 14 days following the implantation (Week -2), patients will have their first in-clinic visit (Week 0 Visit), during which they will begin self-delivered once-daily stimulation using the VNS device, at 60 seconds per stimulation session, pulse width of 250 microseconds, frequency of 10 Hz, and the maximally tolerated output current up to a maximum allowed current of 2.00 mA. Patients will return for weekly visits between Weeks 1-4, at which time outcome and safety assessments will be taken. At each visit between weeks 1 and 4, an attempt will be made to increase (in increments of 0.25 mA) the output current to the maximum level tolerated. At the Week 4 Visit, another attempt to increase the output current will be made and the daily stimulation time will in addition be incremented by 60 seconds to 2 minutes total. At the Week 6 Visit safety and outcome assessments will be taken and another attempt to increase the output current will be made, and the daily stimulation time will in addition be incremented to 5 minutes total. Patients will return at Week 8, at which time safety and outcome assessments will be taken. If the patient has not achieved a clinical remission by CDAI, the frequency of stimulations will increase from once daily to 4 times daily. At Week 12, the patient will return for safety and outcome assessments.The final study visit will be at the Week 16 Visit, at which time patients will have final primary endpoint safety and outcome assessments, including a follow-up endoscopy with endoscopic biopsy. If patients terminate the study prior to week 16, every effort will be made to perform all Week 16 Visit procedures during an Early Termination Visit. Patients who complete the study will have the option to enroll in a long-term extension study. If they do not wish to participate in the extension study they can opt to either have their device permanently inactivated and left in place or have the device surgically explanted.

Intervention

Patients will be asked to delivering vagal nerve stimulator treatments using a small magnet each day during the study. For other see page 17 'Schedule of Assessments' of the study protocol and section E6.

Study burden and risks

See Section E of this form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Male or female subjects aged 18-75 years, inclusive
-Written informed consent prior to any of the screening procedures
-Diagnosis of Crohn's disease for more than 4 months prior to Week -4 Visit, with small bowel and/or colonic involvement
-Current evidence of moderately-to-severely active disease defined by a Week -4 Visit Crohn's Disease Activity Index (CDAI) score of 220 to 450,
inclusive
-Simple Endoscopic Score for Crohn*s Disease evaluation at baseline showing presence of a minimal ulcer score of 2 or 3 in at least 1 segment
-Levels of fecal calprotectin greater than or equal to 200 microgram/gram feces at Week -4 Visit
-History of inadequate response and/or intolerance or adverse events to one or more TNF-alpha inhibitors (e.g., infliximab, adalimumab, or certolizumab pegol) or vedolizumab.
-Female subjects of child-bearing potential are eligible if not pregnant, not planning to become pregnant during the course of the study, and committed to use of contraceptive methods with a failure rate of less than 1 percent per year

Exclusion criteria

Patients who meet any of the following criteria are not to be enrolled in this study:
-Celiac disease
-Diagnosis of ulcerative or indeterminate colitis
-Enterocutaneous, abdominal or pelvic fistulae with abscesses, or fistulae likely to require surgery during the course of the study period
-Bowel surgery, other than appendectomy, within 12 weeks prior to Week -4 Visit and/or has planned surgery or deemed likely to need surgery for Crohn's disease during the study period
-Extensive colonic resection, subtotal or total colectomy
-Presence of ileostomies, colostomies or rectal pouches
-Fixed symptomatic stenoses of small bowel or colon
-History of more than 3 small bowel resections or diagnosis of short bowel syndrome
-Use of prohibited medications inside the specified washout period (prior to Week -4 Visit), and throughout the study.
Prohibited medications include the following:
• TNF antagonists and vedolizumab may continue throughout the study, but treatments should have been given at a stable dose for at least 6 months prior to the screening date and should be maintained at this level throughout the study.
• Use of natalizumab within 8 weeks
• Use of glucocorticoids at doses greater than 10 mg prednisone orally QD, or an equivalent dose of other oral or parenteral glucocorticoids within 4 weeks
• Use of cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil within 4 weeks
• Use of intravenous antibiotics for Crohn's disease within 4 weeks
• Use of parenteral, tube or enteral feeding, or elemental diet within 2 weeks
• Rectal Treatment: Use of 5-aminosalicylates or corticosteroid enemas or suppositories within 2 weeks
• Azathioprine, 6-mercaptopurine and methotrexate can be continued throughout the trial.

These medications must have been used for >12 weeks, at stable dose for at least 3 weeks prior to the Week -4 Visit.
-Leukocytopheresis or granulocytopheresis within 2 weeks prior to Week -4 Visit
-Positive immunoassay for Clostridium difficile at Week -4 Visit
-Known HIV infection
-Known active in infection with HBV or HCV
-Current evidence of, or has been treated for a malignancy within the past five years (other than localized basal cell or squamous cell skin cancer, cervical dysplasia, or any cancer which has been fully staged as in situ and has been fully resected)
-History of evidence of adenomatous colonic polyps that have not been removed.
-Use of any investigational product within 30 days prior to Week -4 Visit for small molecules, or 8 weeks prior for monoclonal antibodies
-Significant psychiatric disease or substance abuse
-History of unilateral or bilateral vagotomy
-History of recurrent vaso-vagal syncope episodes
-Known obstructive sleep apnea
-Known history of cardiac rhythm disturbances, atrio-ventricular block of greater than first degree, or cardiac conduction pathway abnormalities other than isolated right bundle branch block or isolated left anterior fascicle block. Evaluation by a cardiologist is required if the family history, patient history, or electrocardiogram suggests an abnormal cardiac conduction pathway.
-Significant pharyngeal dysfunction or swallowing difficulties
-Pre-existing clinically significant vocal cord damage or hoarseness
-Previously implanted electrically active medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators)
-Asthma or chronic obstructive pulmonary disease not controlled by medications, or any other disease causing clinically significant dyspnea at time of screening
-A greater than or equal to 40 pack-year smoking history
-Active peptic ulcer disease
- Patients with limited life expectancy due to terminal illness

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-11-2014
Enrollment:	3
Type:	Actual

Medical products/devices used

Generic name:	Cyberconics VNS system
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	30-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL49736.018.14